ASSOCIATION OF ESOPHAGEAL SPASM DIAGNOSED BY BARIUM ESOPHAGRAM COMPARED TO ESOPHAGEAL SPASM DIAGNOSED BY HIGH-RESOLUTION ESOPHAGEAL MANOMETRY

by

Kimberly N. Harer

A thesis submitted to Johns Hopkins University in conformity with the requirements

for the degree of Master of Science

Baltimore, Maryland

October, 2018

ABSTRACT

Context: High-resolution esophageal manometry is classically used to evaluate esophageal spasm; however, esophageal spasm is also commonly diagnosed via barium esophagram. It is unknown if spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed on high-resolution esophageal manometry (HREM).

Objective: We aim to evaluate if esophageal spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed on high-resolution esophageal manometry.

Design: Retrospective study of patients who underwent high-resolution esophageal manometry evaluation and had a barium esophagram performed with six months of their esophageal manometry date.

Setting: Outpatient high-resolution esophageal manometry and barium esophagram studies from a single tertiary-care medical center

Patients: 410 adult patients, age 18 and older, who underwent high-resolution esophageal manometry. Of the 410 patients, 212 also underwent barium esophagram within six months of manometry testing and were included in the analysis.

Main Outcome Measures: To evaluate if esophageal spasm diagnosed on high-resolution esophageal manometry is associated with esophageal spasm diagnosed on barium esophagram, measured by the odds ratio comparing the presence or absence of esophageal spasm on high-resolution esophageal manometry with the presence or absence of spasm on barium esophagram. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Results: Patients were divided into spasm on esophageal manometry (SEM) and no spasm on esophageal manometry (NSEM) groups. Of the 212 patients, 23 (10.85%) were included in the SEM group with the remaining 171 (80.66%) included in the NSEM group. Esophagram had a sensitivity of 60.87% (95% CI 38.54-80.29%), specificity of 54.50% (95% CI 47.11-61.74%), PPV of 14.00% (95% CI 10.17-18.96%), and NPV of 91.96% (95% CI 87.12-95.09%) for diagnosis of esophageal spasm compared to HREM.

Multivariable logistic regression model regressing manometry diagnosis of spasm on to esophagram diagnosis of spasm demonstrated an odds ratio of 1.83 [95% CI (0.72-4.62), p=0.2] after adjustment for age, gender, indication for testing, and days between esophagram and manometry testing.

Conclusions: Comparison of esophageal spasm diagnosed on barium esophagram compared to esophageal spasm diagnosed on high-resolution esophageal manometry did not demonstrate a statistically significant association.

Readers:

Dr. Naresh Punjabi

Dr. Pankaj (Jay) Pasricha

ACKNOWLEDGEMENTS

I would like to acknowledge Drs. Jay Pasricha and John Clarke for their past and continued guidance and mentorship. I would also like to thank my parents for their everlasting support and encouragement.

TABLE OF CONTENTS

ABSTRACT ii

ACKNOWLEDGEMENTS iv

LIST OF TABLES vii

INTRODUCTION 1

METHODS 3

Patients 3

Outcomes 3

Data collection 3

Statistical analysis 4

Exploratory data analysis 4

Multivariable logistic regression 5

RESULTS 7

Demographic factors 7

Days between studies 8

Indication for evaluation 9

Spasm severity diagnosed on esophageal manometry 9

Analysis of association of spasm on HREM with spam on esophagram 10

Presence of spasm vs. no spasm on esophagram, compared by HREM diagnosis 11

Analysis considering achalasia type III as a spasm disorder on HREM 12

DISCUSSION 13

REFERENCES ... **17**

APPENDIX 1- STEPWISE VARIABLE SELECTION ... **18**

APPENDIX 2- COLLINEARITY ASSESSMENT ... **18**

APPENDIX 3- INTERACTION ASSESSMENT ... **18**

APPENDIX 4- CONFOUNDING ASSESSMENT ... **19**

APPENDIX 5- DISTRIBUTION OF THE VARIABLE "AGE" ... **19**

APPENDIX 6- ROC CURVE ... **20**

BIOGRAPHY ... **21**

LIST OF TABLES

TABLE 1……………………………………………………………………………7

TABLE 2……………………………………………………………………………7

TABLE 3…………………………………………………………………………..10

TABLE 4…………………………………………………………………………12

TABLE 5…………………………………………………………………………12

INTRODUCTION

Esophageal dysmotility is defined as dysfunction of either lower esophageal (LES) function or esophageal peristalsis.[1] Esophageal peristaltic dysfunction can be further sub-classified into hypercontractile, uncoordinated, and hypocontractile categories based on esophageal manometry measurements. Dysfunction of the LES or esophageal peristalsis can cause disruption of food bolus transit from the oropharynx to the stomach, resulting in symptoms including dysphagia, chest pain, gastroesophageal reflux (GERD), and regurgitation.[2] Despite similar symptoms, each category of dysmotility is characterized by specific abnormalities as defined by the Chicago Classification criteria.[1]

Esophageal spasm consists of two categories: normotensive diffuse esophageal spasm and hypertensive peristalsis disorders, commonly referred to as jackhammer or nutcracker esophagus. Diffuse esophageal spasm is defined as normotensive esophageal peristalsis that is rapidly propagated, and commonly uncoordinated. Hypertensive peristalsis disorders include jackhammer or nutcracker esophagus, which are defined via pressure measurements above a specified threshold as measured on esophageal manometry. Hypocontractile disorders are characterized by absent or weak esophageal peristalsis and include ineffective esophageal motility (IEM) and hypotensive lower esophageal sphincter disorders.[2]

In addition to the aforementioned diseases affecting peristaltic dysfunction, achalasia is a primary dysmotility disorder defined by impaired deglutitive esophagogastric junction (EGJ) relaxation.[1] Although all achalasia variants include failed deglutitive EGJ relaxation, achalasia is further sub-classified by the type of esophageal peristaltic dysfunction that accompanies the EGJ dysfunction. Type I achalasia, classic achalasia, is characterized by significant esophageal hypocontractility. Type II achalasia is characterized by panesophageal pressurization. Finally, type III achalasia is defined by the presence of esophageal spasm.[1]

Esophageal motility disorders have historically been of particular clinical interest due to their clinical manifestations of dysphagia, chest pain, gastroesophageal reflux, and regurgitation. The prevalence and natural history of most esophageal dysmotility disorders are not well understood; however, the prevalence of achalasia has been studied and is estimated at 7.9 to 12.6 per 100,000 population.[3] High-resolution esophageal manometry (HREM) is classically used to diagnose esophageal spasm and hypercontractile disorders based on specific manometric criteria.[1,4] However, barium esophagram is also commonly used to assess bolus transit, and many times is also used to identify esophageal peristaltic abnormalities.[5] Thus, the questions of whether spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed on high-resolution esophageal manometry is raised.

We hypothesize esophageal spasm identified on barium esophagram is not associated with the diagnosis of esophageal spasm as diagnosed on high-resolution esophageal manometry. Evidentiary support for our hypothesis includes prior studies that have been unable to demonstrate an association between radiographic findings on barium esophagram, such as tertiary contractions and gastroesophageal reflux disease, and confirmed disease on esophageal manometry or pH impedance testing.[5-6] This study aims to evaluate these two hypotheses through analysis of a retrospective cohort of esophageal manometry patients

METHODS

Patients

Electronic medical records were identified for adult patients who underwent high-resolution esophageal manometry (HREM) at a single tertiary-care medical center. A total of 410 records were obtained. Only adult patients, age 18 years and older, who underwent a barium esophagram within six months of the HREM study date were included. Patients with a history of prior esophageal surgery were excluded. Patients were not excluded based on indication for evaluation. 212 patients met the inclusion and exclusion criteria.

Outcomes

The primary outcome was to determine if an association is present between esophageal spasm diagnosed on high-resolution esophageal manometry and esophageal spasm diagnosed on barium esophagram. This was determined by calculation of the odds ratio comparing the presence or absence of esophageal spam on barium esophagram with the presence or absence of spasm confirmed on high-resolution esophageal manometry.

Data collection

The health records of the 212 included patients were reviewed. Age, gender, indication for evaluation, date of HREM, results of HREM, date of barium esophagram, and the presence and severity of spasm on barium esophagram were abstracted. If more than one barium esophagram was performed within 6 months of the HREM, the study with the most significant finding of esophageal spasm was selected. If all esophagram studies demonstrated the same findings, the study date closest to the HREM study date was used.

All esophageal manometry studies were read by gastroenterology motility specialists, and diagnoses were made based on the Chicago Classification criteria (v2).[1] Spasm was considered present on manometry if diffuse/distal esophageal spasm (DES), nutcracker esophagus, or jackhammer esophagus were diagnosed.

Specialty trained radiologists read all barium esophagram studies. Barium esophagram findings were reviewed and categorized into either “spasm present” or “spasm absent” groups. Spasm was considered present if the report mentioned the presence of DES, nutcracker esophagus, jackhammer esophagus, or esophageal spasm. The severity of spasm was also recorded if mentioned. Tertiary contractions were not considered spasm.

The indication for evaluation was classified into one of five categories based on common and clinically important indications for esophageal manometry at our institution: dysphagia, chest pain, gastroesophageal reflux disease (GERD)/regurgitation, pre-surgical evaluation, and other. Patients with an indication of hiccups or belching were included in the GERD/regurgitation group. The “other” category included patients who did not have an indication listed or had indications listed as a previously identified esophageal disorder such as scleroderma or hiatal hernia.

Statistical analysis

Exploratory data analysis

Data analysis was performed using the STATA version 13 statistical package (StataCorp LP, College Station, Texas). The dataset was reviewed and did not demonstrate missing data, duplicate records, or values outside the expected range.

A two-tailed t-test was used to compare the means between groups for continuous variables of age and the number of days between the two studies. Fisher's exact tests were performed to compare the SEM and NSEM groups for each of the binary and categorical variables, which included gender, presence/absence of spasm on esophagram, and indication for exam.

Although the indication for testing was recorded as categorical, it was converted to a binary variable for the logistic regression analyses and classified as either a dysphagia or a non-dysphagia indication. The decision to condense the indication categories into either dysphagia or non-dysphagia indications was made to increase statistical power by decreasing the number of categories while maintaining clinically important and relevant indication categories.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Univariable logistic regression models were performed by regressing the outcome variable (manometry diagnosis of spasm) separately onto the predictor variable (spasm on esophagram) and each remaining covariable in order to obtain crude odds ratios and assess the total effect of each variable on the outcome variable. Odds ratios, 95% confidence intervals (CI), and p-values were recorded.

Multivariable logistic regression

A multivariable logistic regression model was then performed with manometry diagnosis of spasm as the outcome variable, diagnosis of spasm on barium esophagram as the predictor variable, and age, gender, indication of dysphagia, and number of days between studies as covariables. Odds ratios, 95% confidence intervals (CI) and p-values were recorded.

The assumption of normality was tested for the continuous variable, age, through visual inspection of side-by-side boxplots comparing the two groups and by the Shapiro-Wilks test. Collinearity was assessed through calculation of variance inflation factors (VIF) after performing a multiple regression analysis in place of the logistic regression model. All VIF values were between 1.0 and 1.1. Likelihood ratio testing was performed to compare numerous logistic regression models. Pearson's goodness-of-fit analysis was used to test the final model due to the limited number of unique covariate combinations-testing demonstrated good fit ($p= 0.452$). Finally, a receiver-operating characteristic (ROC) plot was created of the full logistic regression model to evaluate the model's ability to predict the diagnosis of spasm on manometry.

It is noted that achalasia type III is by definition associated with esophageal spasm per the Chicago Classification guidelines[1]; however, achalasia type III was not included in the primary analysis as it is not commonly considered a spasm disorder. However, given this disorder could hypothetically be seen as spasm on esophagram, an *a priori* sensitivity analysis was planned and performed that included achalasia type III as having spasm diagnosed on esophageal manometry.

Power analysis determined that a total of 61 patients would be needed, power of 80% and alpha 0.5.

RESULTS

Demographic factors

Of the 410 records identified, 212 patients met inclusion criteria and were included in the analysis. The baseline characteristics for the entire cohort of 212 patients are outlined in Table 1.

Table 1: Cohort characteristics of patients who underwent both esophageal manometry and esophagram

	Entire Cohort (n=212)
Age (yrs)*	54.20 (1.06)
Gender	
Male	77 (36.32%)
Female	135 (63/68)
Spasm diagnosed on:	
Esophagram	100 (47.17%)
Manometry	23 (10.85%)
Both	14 (6.60%)

* mean and standard deviation, other variables displayed as n (%)
% days between esophagram and manometry

The 212 patients were divided into two groups based on the presence or absence of spasm noted on HREM. Group 1 had spasm noted on esophageal manometry (SEM group) and group 2 had no spasm noted on esophageal manometry (NSEM group). Demographic, clinical, and radiographic variables were calculated for the SEM and NSEM groups (Table 2).

Table 2: Comparison of patient demographic, clinical, and radiographic characteristics between patients with and without spasm diagnosed on esophageal manometry

	Spasm on Esophageal Manometry (SEM group) (n=23)	No spasm on Esophageal Manometry (NSEM group) (n = 189)	P value#
Age (yrs)*	55.26 (11.81)	54.07 (15.80)	0.73
Male	10 (44%)	67 (35%)	0.49
Indication			0.47
Dysphagia	10 (43.48%)	85 (44.97%)	
Chest pain	0 (0%)	14 (7.41%)	
GERD/regurgitation	7 (30.43%)	61 (32.28%)	
Pre-operative	5 (21.74%)	19 (10.05%)	
Other	1 (4.35%)	10 (5.29%)	
Days between studies*%	35.96 (32.64)	39.19 (33.79)	0.66
Esophagram spasm severity			0.27
None	9 (39.13%)	103 (54.50%)	
Mild	0 (0%)	11 (5.82%)	
Moderate	2 (8.70%)	8 (4.23%)	
Severe	4 (17.39%)	21 (11.11%)	
Present, not quantified	8 (34.78%)	46 (24.34%)	
Manometry spasm disorder			NA
Diffuse esophageal spasm	14 (61%)	NA	
Nutcracker esophagus	5 (22%)	NA	
Jackhammer esophagus	4 (17%)	NA	

* mean and standard deviation. All other variables displayed as n (%)
% days between esophagram and manometry
# fisher's exact analysis for all variables except for age and days between studies (t-test)
+ Lower esophageal sphincter

Of the 212 patients, 23 (11%) were included in the SEM group with the remaining 189 (89%) were included in the NSEM group. Within the 23 SEM group patients, 14 (61%) had diffuse esophageal spasm, 5 (22%) had nutcracker esophagus, and 4 (17%) had jackhammer esophagus on HREM.

After dividing patients into groups based on the presence or absence of a spasm disorder diagnosed on HREM, demographic factors between the two groups were compared. The mean age for the SEM group was 55.26 (SD 11.81) with a range of 25 to 71 years old, and the mean age for the NSEM group was 54.07 (SD 15.80) with a range of 18 to 92 years old. A t-test comparing group mean ages did not demonstrate a statistically significant difference between groups ($p=0.73$). Normality testing was performed by visual inspection of side-by-side boxplots comparing the SEM and NSEM groups and demonstrated approximately normal distributions in both groups (Appendix 5). The Shapiro-Wilks test for age was also performed and was consistent with a normal distribution ($p=0.121$).

Both patient groups consisted predominantly of females, with the SEM group including 10 males (44%) and the NSEM group including 67 males (35%). Fisher's exact test did not demonstrate a statistically significant difference between the two groups ($p=0.49$).

Days between studies

Although patients were included if their esophagram occurred within 6 months of esophageal manometry measurements, the mean number of days between barium esophagram and esophageal manometry was significantly less than the allowed 6-month timeframe. The mean number of days between studies was 35.96 (SD 32.64) for the SEM group, with a range of 0 to 121 days. Similarly, the mean number of days between barium esophagram and esophageal manometry was 39.19 (SD 33.79) for the NSEM group, with a range of 0 to 154 days. A t-test comparing means between the two groups did not demonstrate a statistically significant difference (p=0.66).

Indication for evaluation

Regarding the indication for evaluation, dysphagia was the most common indication for testing in both groups, accounting for 43.48% of the SEM group and 44.97% of the NSEM group. GERD/regurgitation was the second most common indication in both groups contributing 30.43% and 32.28% in the SEM and NSEM categories respectively. The remaining indications, including chest pain and pre-operative evaluation, were less common (Table 2). T-test analysis did not demonstrate a statistically significant difference between groups (p=0.47).

Spasm severity diagnosed on esophageal manometry

The presence/absence and severity of esophageal spasm noted on barium esophagram were determined for both the SEM and NSEM groups. 39.13% of the SEM group and 54.50% in NSEM group did not have spasm concomitantly diagnosed on barium esophagram. Regarding severity of esophageal spasm if identified on esophagram, severe spasm was diagnosed in 17.39% of the SEM group and 11.11% of the NSEM group, moderate spasm was diagnosed in 8.70% of the SEM group and 4.23% of the NSEM group, and mild spasm was diagnosed in 0% of the SEM group and 5.82% of the NSEM group. In 34.78% of the SEM group and 24.34% of the NSEM group, spasm was noted on esophagram without quantification of the severity. There was not a significant difference between groups (p=0.27).

Analysis of association of spasm on HREM with spam on esophagram

Of the 212 total patients, 23 (10.85%) were diagnosed with spasm on HREM and 100 (47.17%) were diagnosed with spasm on barium esophagram. 14 (6.60%) were diagnosed with spasm on both HREM and esophagram. If HREM is considered the gold standard for evaluating the presence of esophageal spasm, barium esophagram had a sensitivity of 60.87% (95% CI 38.54-80.29%), specificity of 54.50% (95% CI 47.11-61.74%), positive predictive value (PPV) of 14.00% (95% CI 10.17-18.96%), and negative predictive value (NPV) of 91.96% (95% CI 87.12-95.09%).

To further evaluate if esophageal spasm diagnosed on manometry is associated with esophageal spasm diagnosed on esophagram, logistic regression analyses were performed. Univariable logistic regression models regressing a diagnosis of spasm on HREM on to each covariate demonstrated the following crude odds ratios and p-values: spasm diagnosed on esophagram (OR 1.86, p= 0.16), age (OR 1.00, p=0.73), gender (OR 0.71, p=0.45), indication of dysphagia (OR 0.94 p=0.90), and days between studies (OR 1.00, p=0.66) (Table 3).

Table 3: Esophageal spasm diagnosed on esophagram: crude and adjusted odds ratios for univariable and multivariable logistic regression models

	Crude Odds Ratio (95% CI)	P value	Adjusted* Odds Ratio (95% CI)	P value
Spasm on esophagram	1.86 (0.77-4.51)	0.16	1.83 (0.72-4.62)	0.20
Age (yrs)	1.00 (0.98-1.03)	0.73	0.99 (0.97-1.03)	0.99
Gender (M:F)	0.71 (0.30-1.7)	0.45	0.73 (0.30-1.76)	0.48
Indication dysphagia^{+}	0.94 (0.39-2.25)	0.90	0.91 (0.38-2.21)	0.84
Days between studies	1.00 (0.98-1.01)	0.66	1.00 (0.98-1.01)	0.78

* Adjusted model includes spasm on esophagram, age, gender, indication of dysphagia, and days between studies
+ yes versus no dysphagia

Collinearity testing was performed, including all variables used in the univariable models, through variance inflation factor (VIF) testing. VIF values ranged from 1.0 to 1.1, indicating no collinearityty (Appendix 2).

A multivariable logistic regression model was then performed regressing manometry diagnosis of spasm on esophagram diagnosis of spasm with adjustment for age, gender, indication of dysphagia, and days between studies. The odds ratio for spasm on esophagram was statistically insignificant at 1.83 ($p=0.2$) (Table 3). Pearson's goodness-of-fit analysis demonstrated good fit ($p= 0.42$).

The receiver-operating characteristic (ROC) plot of the full model was performed and demonstrated an area under the curve (AUC) of 0.5973, indicating poor accuracy to predict esophageal spasm (Appendix 6).

Presence of spasm vs. no spasm on esophagram, compared by HREM diagnosis

Patients were then divided into two groups: patients with spasm diagnosed on esophagram and patients without spasm diagnosed on esophagram. The two groups were compared by the results of the HREM findings (Table 4). No statistically significant difference was identified; however, inspection of the data demonstrated all patients with achalasia type III (spastic achalasia) were found to have spasm on esophagram. It was also noted that 24% of patients in both groups consisted of patients who were diagnosed with hypocontractile disorders on esophageal manometry, such as failed or absent peristalsis.

Table 4: Esophagram spasm vs. no spasm, compared by HREM diagnosis

	No spasm on Esophagram (n=112)	Spasm on Esophagram (n = 100)	P value
HREM diagnosis			0.2
Normal manometry	26 (23.21%)	19 (19%)	
Achalasia type I and II*	17 (15.18%)	13 (13%)	
Achalasia type III	0 (0.00%)	4 (4%)	
Distal/diffuse esophageal spam	4 (3.57%)	10 (10%)	
Jackhammer esophagus	3 (2.68%)	1 (1%)	
Nutcracker esophagus	2 (1.79%)	3 (3%)	
Hypertensive LES+	1 (0.89%)	3 (3%)	
Failed /absent peristalsis	27 (24.11%)	24 (24%)	
EGJ outflow obstruction^	5 (4.46%)	4 (4%)	
Other non-spasm finding#	27 (24.11%)	19 (19%)	

* type II achalasia was separated as type III achalasia is associated with esophageal spasm
\# examples include non-spasm disorders such as hypotensive LES and hiatal hernia
\+ LES= lower esophageal sphincter
^ EGJ = esophagogastric junction

Analysis considering achalasia type III as a spasm disorder on HREM

Given achalasia type III is by definition associated with the presence of esophageal spasm and could hypothetically be visualized as spasm on esophagram, *a priori* sensitivity analysis including achalasia type III as having spasm on HREM was planned. Four of the 212 patients had a diagnosis of achalasia type III. The multivariable logistic regression was performed including achalasia type III as having spasm on HREM. No statistically significant association was identified; however, the OR for spasm diagnosed on esophagram trended towards significance. The results are outlined in Table 5.

Table 5: Esophageal spasm diagnosed on esophagram, including type III achalasia patients: adjusted odds ratios for multivariable logistic regression models

	Adjusted* odds ratio for original analysis (95% CI)	P value	Adjusted* odds ratio including achalasia type III (95% CI)	P value
Spasm on esophagram	1.83 (0.72-4.62)	0.20	2.25 (0.92-5.52)	0.07
Age (yrs)	0.99 (0.97-1.03)	0.99	1.00 (0.98-1.03)	0.84
Gender (M:F)	0.73 (0.30-1.76)	0.48	0.64 (0.28-1.47)	0.30
Indication dysphagia+	0.91 (0.38-2.21)	0.84	1.23 (0.53-2.83)	0.63
Days between studies	1.00 (0.98-1.01)	0.78	1.00 (0.99-1.01)	0.99

* Adjusted model includes spasm on esophagram, age, gender, indication of dysphagia, and days between studies
\+ yes versus no dysphagia

DISCUSSION

Although esophageal spasm is typically diagnosed via high-resolution esophageal manometry, esophageal spasm is also commonly diagnosed by clinicians on barium esophagram. Despite this, no prior study has studied if esophageal spasm diagnosed on esophageal manometry is associated with spasm diagnosed on barium esophagram. This study aimed to evaluate if spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed on high-resolution esophageal manometry (HREM). The findings from this retrospective study support our hypothesis that the diagnosis of spasm on barium esophagram is not associated with the diagnosis of esophageal spasm on HREM. Despite controlling for potential confounders of age, gender, indication for exam, and the number of days between exams, there was not a statistically significant association between spasm on esophagram and spasm on HREM.

This study's finding that esophageal spasm diagnosed on esophagram is not associated with esophageal spasm diagnosed on HREM is a clinically relevant discovery as this raises concerns regarding if esophageal spasm diagnosed on barium esophagram is clinically important esophageal spasm that is not being identified based on HREM manometric thresholds. It is possible that some patients with esophageal spasm identified on barium esophagram may simply have esophageal hypercontractility that fails to meet the manometric criteria required to diagnose esophageal spasm on HREM. This hypothesis then raises the question if these milder contractions are clinically relevant or if they represent a pre-spasm condition.

Although further questions are raised and additional studies need to be conducted, the lack of association identified in this study suggests that patients with suspected esophageal spasm should undergo HREM testing. Additionally, patients who undergo barium esophagram and are incidentally found to have esophageal spasm without associated clinical symptoms, the argument can be made that further testing with HREM is likely not necessary and a poor utilization of resources. However, symptomatic patients regardless of if spasm is identified on esophagram should certainly be further evaluated for spasm and other esophageal motility disorders with HREM. Although the NPV of esophagram was 91%, HREM is still recommended to evaluate for esophageal dysmotility in symptomatic patients given the clinical symptoms of spasm have significant overlap with other clinically relevant esophageal dysmotility disorders.

Interestingly, an indication of dysphagia did not demonstrate a statistically significant association with spasm compared to non-dysphagia indications. This finding is likely due to a true lack of association; however, it could be due to the retrospective nature of the study and the dependence on the prior documentation habits of clinical staff. The lack of association may also be due to the fact esophageal spasm diagnosed on esophagram is a subjective diagnosis, whereas esophageal spasm on manometry is an objective measure based on standardized pressure thresholds.

This study has many strengths. Despite the retrospective observational design, there were no statistically significant differences between the two groups in age, gender, indication for testing, or number of days between exams. The dataset also included a patient population that represented a broad range of indications for exam, but it still contained a large sub-set of the most common and clinically significant indication of dysphagia. This diversity afforded an analysis of the association between indication and the diagnosis of spasm on esophagram. Additionally, a select few gastroenterologists specifically trained in esophageal motility read the esophageal manometry studies, and they all used the same standardized manometric criteria for diagnosis. This created consistency and uniformity within the study. Finally, although a six-month window between studies was allowed, the mean number of days between studies was only 38.84. This short timeframe decreases the possibility the patient's disorder activity changed between studies resulting in inaccuracy of the analysis comparing the two tests.

This study also had some weaknesses. As mentioned above, esophageal spasm diagnosed on esophagram is a subjective diagnosis, whereas esophageal spasm on manometry is an objective diagnosis based on standardized manometric thresholds. Additionally, although the time between studies was relatively short, the retrospective nature of this study resulted in comparison of two different studies not performed on the same day. It is possible a hypercontractile disorder may have been more active during one study than the other study. However, it is unlikely that a patient with a true hypercontractile disorder would have a normal manometry exam without any evidence of spasm identified on the study. Additionally, if a patient is still undergoing testing, it can be presumed the patient's symptoms are still present and the underlying disorder is still active. Finally, this study was retrospective with a small sample size of patients having a diagnosis of spasm on HREM. A larger prospective study would certainly be beneficial to obtain more detailed symptom data, standardize study protocols, obtain and compare objective data for both modalities (i.e. conduction velocity), and limit information bias caused by studies being performed weeks apart.

The findings from this study help answer the clinical question if esophageal spasm diagnosed on barium esophagram is associated with esophageal spasm diagnosed on esophageal manometry. These data support our hypothesis that spasm diagnosed on barium esophagram is not associated with spasm diagnosed on HREM. Additionally, the ROC analysis demonstrated poor predictive value of spasm on esophagram to predict spasm on HREM. Although an association was not demonstrated by this study, it is important to understand these findings specifically apply to esophageal spasm and should not be extrapolated to other esophageal dysmotility disorders or esophageal structural diseases.

In conclusion, this study demonstrates esophageal spasm diagnosed on barium is not associated with esophageal spasm diagnosed on high-resolution esophageal manometry. Given the lack of association identified in this study, additional clinically important questions are raised about the diagnosis of esophageal spasm, including if the current HREM diagnostic thresholds fail to detect clinically relevant esophageal spam and hypercontractility. Further prospective studies need to be performed to further evaluate this association and the clinical relevance of esophageal spasm diagnosed on barium esophagram.

REFERENCES

1. Kahrilas P, Brendenoord J, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27;160-174.
2. Paterson W, Goyal R, Fortunee I. Esophageal motility disorders. GI Motility Online. 16 May 2006. doi:10.1038/gimo20. Online. http://www.nature.com/gimo/contents/pt1/full/gimo20.html. Accessed 05/01/15
3. Lacy B, Weiser K. Esophageal Motility Disorders Medical Therapy. J Clin Gastrtoenterol. 2008;42(5):652-658
4. Muller M. Impact of high-resolution manometry on achalasia diagnosis and treatment. Ann Gastroenterol. 2015; Jan-Mar28(1): 3-9.
5. Halland M, Ravi K, Barlow J, Arora A. Correlation between the radiological observation of isolated tertiary waves on esophagram and findings on high-resolution esophageal manometry. Diseases of the Esophagus. 2014 0ct 20. [Epub ahead of print]
6. Cho Y, Choi M, et al. Comparison of bolus transit patters identified by esophageal impedance to barium esophagram in patients with dysphagia. Diseases of the Esophagus. 2012;25;17-25

APPENDIX 1- STEPWISE VARIABLE SELECTION

Backwards and forwards stepwise variable selection was performed as a sensitivity analysis. Spasm on esophagram was forced into the model. All other covariates were removed during the analysis, leaving only spasm on esophagram remained. This was consistent with the findings from our selected model.

APPENDIX 2- COLLINEARITY ASSESSMENT

Collinearity testing was performed including all variables included in the univariable models, and demonstrated variance inflation factors ranging from 1.10-1.00. These results suggested the variables were not collinear.

Variable	VIF
Spasm on esophagram	1.10
Age	1.09
Days between studies	1.02
Indication	1.01
Gender	1.00
Mean VIF	**1.04**

APPENDIX 3- INTERACTION ASSESSMENT

We hypothesized that the number of days between studies may be modified by indication. Dysphagia symptoms tend to prompt a more expedited evaluation than non-dysphagia symptoms, and we hypothesized patients with dysphagia would have fewer number of days between tests than non-dysphagia patients. An interaction term was created and logistic regression analysis was performed. Analysis did not demonstrate indication modified the number of days between studies ($p > 0.05$).

APPENDIX 4- CONFOUNDING ASSESSMENT

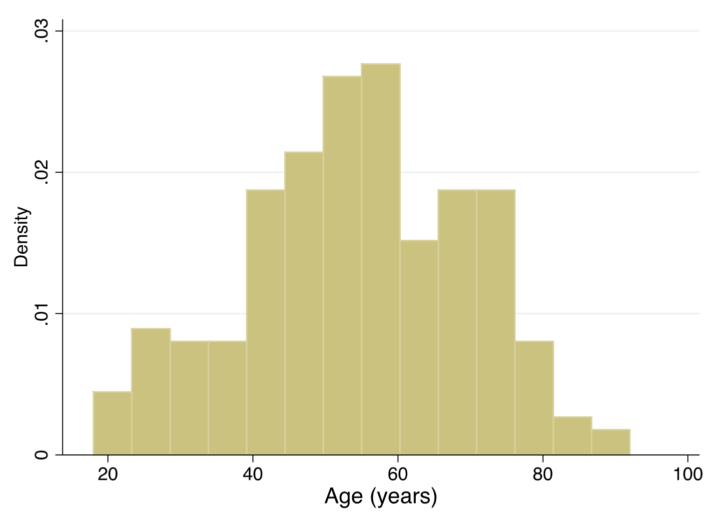
Confounding was assessed by comparing crude and adjusted odds ratios. The crude and adjusted odds ratios were similar. The table below (Table 3 from main text) compares the crude and adjusted odds ratios for the full model.

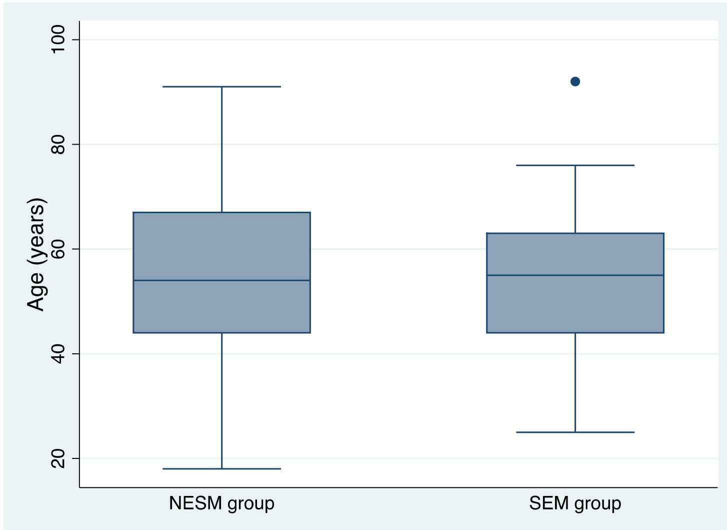
Table 3: Esophageal spasm diagnosed on esophagram: crude and adjusted odds ratios for univariable and multivariable logistic regression models

	Crude Odds Ratio (95% CI)	P value	Adjusted* Odds Ratio (95% CI)	P value
Spasm on esophagram	1.86 (0.77-4.51)	0.16	1.83 (0.72-4.62)	0.20
Age (yrs)	1.00 (0.98-1.03)	0.73	0.99 (0.97-1.03)	0.99
Gender (M:F)	0.71 (0.30-1.7)	0.45	0.73 (0.30-1.76)	0.48
Indication dysphagia+	0.94 (0.39-2.25)	0.90	0.91 (0.38-2.21)	0.84
Days between studies	1.00 (0.98-1.01)	0.66	1.00 (0.98-1.01)	0.78

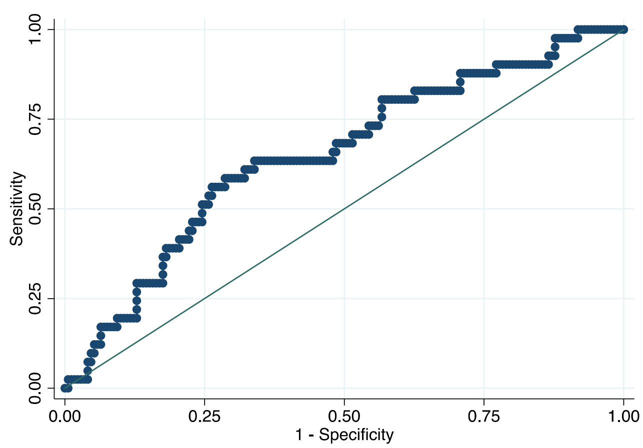
* Adjusted model includes spasm on esophagram, age, gender, indication of dysphagia, and days between studies
+ yes versus no dysphagia

APPENDIX 5- DISTRIBUTION OF THE VARIABLE "AGE"





APPENDIX 6- ROC CURVE



BIOGRAPHY

Kimberly Nicole Harer was born on June 19, 1983 in Hoven, South Dakota. She attended a two-room country school from kindergarten through grade six, where she was the only student in her class. She completed middle school and high school in Gettysburg, SD, followed by completion of baccalaureate degrees in Biology and Microbiology at South Dakota State University. Following baccalaureate degree achievement in 2006, she earned her medical degree from Sanford School of Medicine/University of South Dakota in 2010. From 2010 to 2014, Dr. Harer completed Internal Medicine Residency at Mayo Clinic in Rochester, Minnesota. Driven by a love for medicine and research, as well as a desire to experience the east coast, she completed a clinical and research Gastroenterology Fellowship at Johns Hopkins Hospital with simultaneous enrollment in the Graduate Training Program in Clinical Investigation at Johns Hopkins Bloomberg School of Public Health. She currently specializes in Gastroenterology Motility at the University of Michigan, where she enjoys her work in both clinical medicine and translational research.